STUDIES ON RELATIONS BETWEEN INSULIN SENSITIVITY AND LIVER GLYCOGEN IN TOTALLY DEPANCREATIZED DOGS

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by

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I. INTRODUCTION

Since Rockey performed for the first time an operation of total pancreatectomy for pancreatic cancer in 1943, many successful illustrations of total pancreatectomy for pancreatic cancer, neoplasms of Langerhans' islet cell, chronic pancreatitis with pancreaticolithiasis and other cases have been reported. As the patho-physiology of totally pancreatectomized state, diabetes mellitus, development of fatty liver, disturbance of digestion and absorption, etc. are enumerated, but many pending problems remained still to be solved.

History of study on diabetes due to pancreatectomy was old and development of diabetes after total pancreatectomy was already acknowledged by v. Mering & Minkowski in 1889. As "Insulin" was found by Best & Banting in 1922, many investigators have been trying to study the diabetic state following total pancreatectomy. Bliss, Fisher, Allan, Bowie, Robinson and Macleod and others reported that the depancreatized dogs could not maintain their normal body weight and die, despite the insulin control of the hyperglycemia and the glycosuria; and a marked accumulation of fat in the liver was found to be the most prominent change in these dogs at autopsy. After a while Dragstedt stated that the totally depancrea-

tized dogs required a less amount of insulin than the partially depancreatized dogs or the alloxan-administered diabetic dogs. Furthermore he observed that in the depancreatized dogs, as time went on, there occurred a steadily lessening excretion of dextrose, in spite of continuously decreasing doses of insulin, until after six to eight weeks, the animals required only from 2 to 3 units of insulin, and the larger amount of sinsulin, even 5 units, might at this time provoke fatal hypoglycemic convulsions. He thought that this phenomenon was due to an increase of sensitivity toward insulin, and was caused by the development of fatty liver after total pancreatectomy.

Then, SOSKIN & LEVINE stated that the depancreatized dogs which had no disturbance of liver function were sensitive ("juvenile" or unstable) toward insulin and showed rapid falling of blood sugar level by insulin test; they also said that the depancreatized dogs which had an advanced degree of fatty liver were insensitive ("adult" or stable) toward insulin, and their status of diabetes was mild requiring the lesser amount of insulin, and that, in these dogs, the falling of blood sugar level was by far in lower degree by insulin test.

Authors reporting complete pancreatectomy of human beings declared, on the basis of insulin requirements, that insulin sensitivity increased after the operation.

Contrary to these opinions stated above, HONJO & AOKI in our clinic explained that the fatty liver after total pancreatectomy could scarcely be found in human beings or in dogs. Moreover, OSHITANI and YAMAMOTO studied in detail on the early and the late type of fatty liver in dogs respectively and they ascertained the fact that, throughout all the periods after total pancreatectomy, the development of the fatty liver could be prevented effectually by the use of an adequate dosage of insulin. On the other hand, KAWAMURA in our same clinic pointed out that the depancreatized dogs tended to have a decreased sensitivity in insulin test and reported that in only a few cases, 4 of 23 dogs, the amount of insulin administered had to be reduced at the later time after the operation. Thus, the development of fatty liver by which an increase of insulin sensivitity seemed to be caused, could possibly be avoided by the adequate administration of insulin; and it became clear that the sensitivity toward insulin, contrary to the general opinion, was lowered after total pancreatectomy.

On the other hand, there exists an irrefragable fact that the depancreatized dogs are apt to have an attack of hypoglycemic signs even by a small dose of insulin. To make clear these phenomena which looked like contradicted with each other, I have done the following experiments to prove what changes would occur in the amount of liver glycogen and what relationship might reside between these changes and the insulin sensitivity.

II. EXPERIMENTAL MATERIALS AND METHODS

The adult dogs, about 10 kg in weight, were used. These dogs were fed by rice with a mixture of fish and vegetable about 150g—200g, fish bone or meat, about 20g—30g; and raw pancreas and methionine were not given in parti-

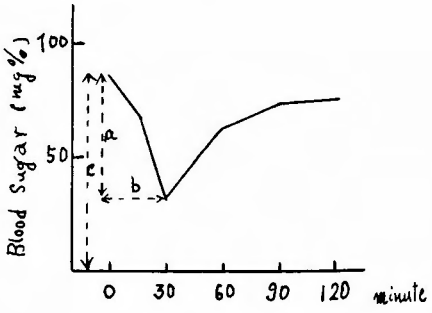
cular. The venous blood was taken from hind limbs, and its blood sugar level was examined. Small pieces of the liver were taken by laparotomy, and their glycogen content was measured.

The pancreas could be carefully removed without much difficulties in dogs by cutting off the pancreatic branches of the pancreaticoduodenal artery and vein under double ligation and by separating and cutting the main pancreatic duct after double ligation. Regular insulin was always used both for the treatment and for the insulin test. The amount of insulin to be injected for insulin test was so little that it was diluted with the solvent provided by Japanese pharmacopoeia, in order to be accurate. SOMOGYI-NELSON's method was applied to examine the level of blood sugar by using 1.0 cc of blood.

The amount of liver glycogen was measured numerically according to GOOD-KRAMER-SOMOGYI's method. As liver glycogen in a living body was very unstable, I used an anesthetic such as chlorpromazine or pantbarbital which did not provoke the destruction of glycogen during laparotomy, and put the specimens into boiling alkali solution (30% KOH) as soon as possible.

There were various methods to perform insulin test and various theories were stated to indicate insulin sensitivity. I determined insulin sensitivity by adopting NORGAARD-THAYSEN's assimilation index under the same opinion as KAWAMURA's in our clinic. Assimilation index was calculated from the curve of blood sugar level according to NORGAARD-THAYSEN illustrated in Fig. 1. Early in the morning when the dogs feel hungry, 0.1-0.3 units of regular insulin per kg in body weight was injected intravenously and blood was taken every 30 minutes. In this way, blood sugar levels were measured from 4 hours to 6 hours after the injection of insulin. In addition to performing the above insulin test, I injected 1.0-2.0 units of insulin per kg in body weight intravenously to one group of dogs and subcutaneously to another group, and then examined thus acquired blood sugar curves.

Measurement of liver glycogen was concurrently performed with insulin test for some group. As time went on after total pancreatectomy, however, the dogs operated on began to show hypoglycemic signs; and after the fourth postoperative week, it was difficult to carry out the insulin test and the measurement of liver glycogen at the same day in almost all cases. But, to make sure the relationship between assimilation index and liver glycogen content, these two experiments were performed at intervals of 2 or 3 days.



$$\text{Assimilation Index} = \frac{a}{b} \times \frac{100}{C}$$

Fig. 1 Calculation of Assimilation Index (NORGAARD and THAYSEN)

III. RESULTS

1. Insulin Test and Liver Glycogen in Normal Dogs

The blood sugar level of normal dogs in my experimental series ranged in the state of fasting between 89 mg % in maximum and 63 mg % in minimum.

When the insulin test was performed in normal dogs in the state of fasting, the blood sugar dropped to its lowest level 30-60 minutes after injection, and then it rose up rapidly and 90-120 minutes later, restored to the former level before injection, as illustrated in Fig. 2. In this case, 0.1 to 0.3 units of insulin were injected intravenously per kg in body weight in insulin test. If 2.0 units of

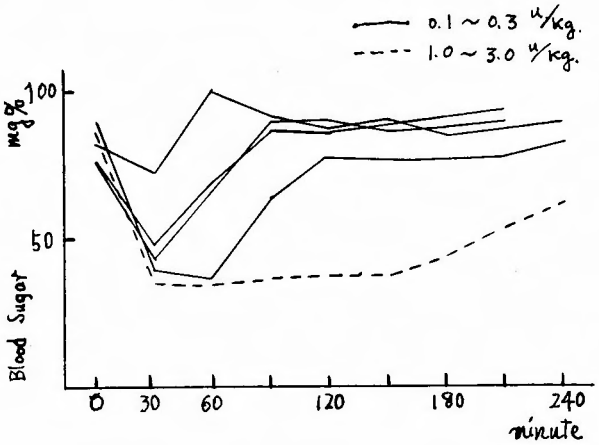


Fig. 2 Blood Sugar Curves after Insulin Injection in Normal Dogs. (Dose of Insulin: 0.1~0.3 or 1.0~3.0 u/kg Intravenously Injected)

Table 1 Blood Sugar Level, Assimilation Index and Liver Glycogen Content in Fasting Normal Dogs

Dog No.	Body Weight	Blood Sugar	Assimilation Index	Liver Glycogen Content
3	7.0kg	86mg%	0.51	5,730mg%
4	13.0	75	1.47	—
5	8.3	82	1.42	6,080
6	8.0	84	1.44	—
7	13.0	88	1.97	4,018
10	9.3	89	1.27	7,058
11	10.0	78	1.62	4,588
12	8.5	84	—	4,937
15	7.5	74	1.89	1,518
17	11.0	67	0.75	6,546
18	8.6	63	—	2,650
21	7.3	87	—	6,375

insulin were injected intravenously per kg in body weight, the blood sugar level was found to drop at the same rate as the case stated above, as BODANSKI, SCOTT and SOMOGYI had already proved, reaching its lowest level 60 minutes after injection, but it continued to keep this low level for longer time. 0.5-2.0 were obtained if the assimilation index was calculated from the curve of blood sugar which was acquired by insulin test with the injection of 2.0 units of insulin per kg in body weight.

Liver glycogen content of normal dogs was 7.058 mg % in maximum and 1.518 mg % in minimum under the state of fasting early in the morning. (Table 1 & Fig. 9) Almost all dogs showed 5%-7%.

2. Insulin Test and Liver Glycogen in Totally Depancreatized Dogs

The dogs showed hyperglycemia at once when total pancreatectomy was performed. Blood sugar level of the dogs in the early morning was controlled at about 200 mg % or so, by using insulin for this hyperglycemia. In my studies, the blood sugar in the depancreatized dogs was adjusted by the administration of 2.0 units of insulin per kg in body weight. Hypoglycemic signs appeared in about a half out of twelve dogs which were living for a long time. Within three weeks after total pancreatectomy, the depancreatized dogs seldom showed hypoglycemic signs by the supply of a sufficient amount of food even if 5.0 units of insulin per kg in body weight were given, but after 4 weeks, hypoglycemic signs were presented very often two hours or more after the administration of insulin. When hypoglycemia set in, the depancreatized dogs became unconcerned about their circumstances or too sensitive to surroundings. The dogs, in some cases, driveled and barked; moreover, convulsions took place in extremities, and in masticatory and neck

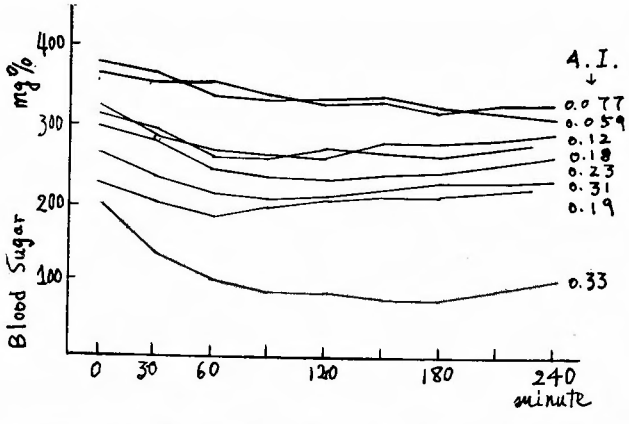


Fig. 3 Blood Sugar Curves and Their Assimilation Indices after Insulin Injection in Totally Depancreatized Dogs at 3rd Week after Operation (Dose of Insulin: 0.1~0.3 u/kg Intravenously Injected)

muscles. At this moment, blood sugar was shown to be markedly decreased.

i) Insulin Test (Insulin 0.1-0.3 u/kg) at The 3rd Week after Total Pancreatectomy

At the 3rd week after total pancreatectomy in the period when hypoglycemic convulsions seldom occurred, the curve of blood sugar level by insulin test was very much different from that of normal dogs as shown in Fig. 3. In other words, the level of blood sugar took much time to reach its minimum point and it was too slow to be back to the initial value before the injection. Therefore, the assimilation index was low in contrast with that of normal dogs, showing within 0.06-0.33. Considering from the assimilation index, the depancreatized dogs proved to be insensitive to insulin than normal dogs.

ii) Insulin Test (Insulin 1.0-3.0 u/kg) at The 3rd Week after Total Pancreatectomy

In normal dogs, when the following two cases were compared with each other in insulin test, one was injected 0.1-0.3 units of insulin per kg in body weight and the other was injected 1.0-3.0 units of insulin per kg in body weight, there were no differences between the two in a descending loop of the blood sugar curve.

But, in the case of the depancreatized dogs, I obtained somewhat different findings. 1.0-3.0 units of insulin per kg in body weight were injected intravenously to one group and also were injected subcutaneously to the other group at the 3rd week after total pancreatectomy and, the curves of the blood sugar levels were made respectively. These two curves were compared with that obtained by the intravenous injection of 0.1-0.3 units of insulin per kg of body weight. While the curves of the former showed a gradual dropping in both cases, they showed much lower values at the bottom of them than that of the latter. As shown in Fig. 4 & 5,

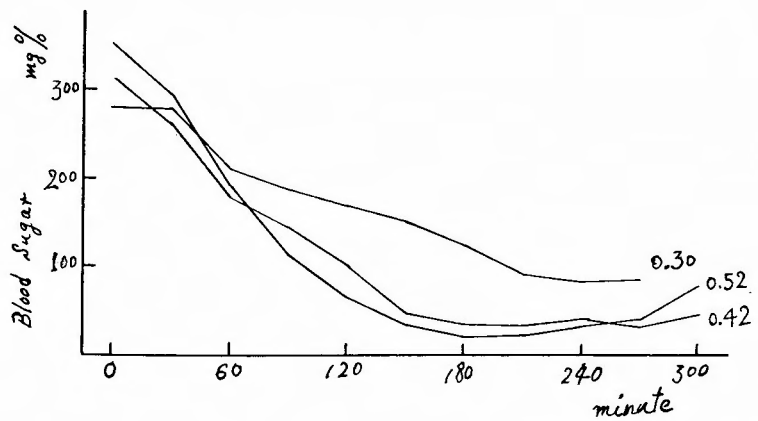


Fig. 4 Blood Sugar Curves and Their Assimilation Indices Obtained from Totally Depancreatized Dogs at 3rd Week after Operation
(Dose of Insulin: 1.0~3.0 u/kg Intravenously Injected)

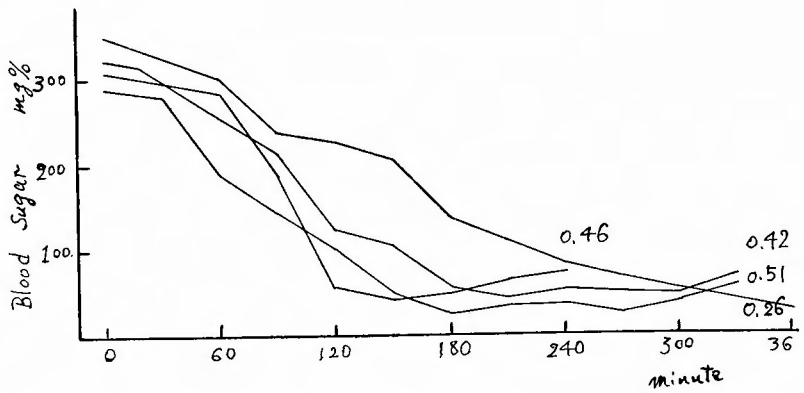


Fig. 5 Blood Sugar Curves and Their Assimilation Indices Obtained from Totally Depancreatized Dog at 3rd Week after Operation
(Dose of Insulin: 1.0~3.0 u/kg Subcutaneously Injected)

their values fell down to the same points as those of normal dogs injected by either 0.1-0.3 or 1.0-3.0 units of insulin per kg in body weight. But hypoglycemic symptoms were not always developed. When the group injected intravenously was compared with that injected subcutaneously, their blood sugar curves showed almost the same attitude in both of them until they reached the lowest level, and then, the curve of the former showed an ascending tendency while that of the latter kept the lowest level for a fairly long time. When the assimilation index was calculated in two groups stated above, 0.3-0.52 were obtained in the former group, and 0.26-0.51 in the latter. These values were almost the same as these of the group which was given 0.1-0.3 units of insulin per kg in body weight. In Table 2, the assimilation indices in each cases measured at the 3rd week after total pancreatectomy were shown.

iii) Liver Glycogen at The 3rd Week after Total Pancreatectomy

In the determination of liver glycogen contents at the 3rd week after total pancreatectomy, I placed much importance in evaluating the influenec of the amount of insulin given daily for the treatment of diabetes.

The dogs were divided into two groups; one was given a large amount of insulin and the other a small amount of it. In other words, every day after total pancreatectomy, 3.0-5.0 units of regular insulin per kg of body weight was injected subcutaneously in the former group and 1.0 units in the latter. Between these two groups, there were no remarkable differences in the

Table 2 Assimilation Indices in Totally Depancreatized Dogs At 3rd Week after Operation

0.1~0.3u/kg Intravenously	1.0~2.0u/kg Intravenously	1.0~2.0u/kg Subcutaneously
0.33	0.52	0.51
0.31	0.42	0.46
0.23	0.30	0.42
0.19		0.26
0.18		
0.12		
0.077		
0.059		

blood sugar level in the state of fasting early in the morning; and 200 mg% or so were kept. But the marked differences were proved in liver glycogen contents between them at the 3rd week after total pancreatectomy. Namely, in six dogs of the former group, all of them indicated the values more than 1,300 mg % and ranging within the physiological limits, but five dogs out of six in the latter group showed the much lower values, as shown in Table 3.

On the other hand, in the experiment of OSHITANI in our clinic, it was demonstrated that in case of the administration of high units of insulin (5.0 u/kg) the amount of liver fat was kept within normal limits until at least about the 3rd week following total pancreatectomy. Therefore, if a large amount of insulin is given, it can be said that the contents of both glycogen and fat in the liver are maintained in normal level until the end of the 3rd week after total pancreatectomy, and that the insulin sensitivity is lowered.

iv) Comments on i), ii), and iii)

The results of insulin test and liver glycogen determination at the 3rd week after total pancreatectomy were stated above. Then I tried to examine what relationships there were between liver glycogen contents and insulin sensitivity at the same period after total pancreatectomy. With respect to insulin sensitivity, there could be seen no relationships between the group to which a large amount of insulin was administered and the group to which a small amount of insulin was given. Therefore, as shown in Table 3, there were no relationships to be mentioned between the insulin sensitivity and the liver glycogen contents.

In order to measure the liver glycogen contents, it is necessary to perform surgical procedures, such as narcosis and laparotomy. The group to which a large amount of insulin was administered showed a resistance against the surgical procedure.

Table 3 Assimilation Indices and Liver Glycogen Contents in Groups to which High or Low Units of Insulin were Administered

	Dog No.	Body Weight	Assimilation Index	Liver Glycogen		Differential Ratio
				Before	After	
Insulin High Unit Giving Group	A 2	10.0kg	0.077	1,970mg%	2,280mg%	+19.46%
	A 3	14.0	0.33	1,748	3,265	+86.7
	A 5	10.3	0.059	1,531	1,363	−11.0
	A 7	8.5		2,131		
	A 8	11.0	0.23	3,082	3,321	+ 7.8
	A10	9.0	0.16			
Insulin Low Unit Giving Group	B 1	13.0	0.18	241	246	+ 2.1
	B 3	9.5		2,472	2,762	+11.7
	B 4	7.3	0.31	578	357	−38.2
	B 6	12.0	0.19	482	396	−17.8
	B 7	10.0	0.12	451		
	B 8	8.5		372		

In other words, this group, viz. the group which had a large amount of hepatic glycogen, restored its health in a short time and seemed to have a good appetite. On the contrary, in the group to which a small amount of insulin was administered, recovery to its initial condition delayed and, in severe cases, the effect of anesthesia was continued for more than ten hours after the surgery.

At the 3rd week after total pancreatectomy, the insulin test was performed by an intravenous injection of 0.2 u/kg insulin, and, at the same time, measured the amount of hepatic glycogen before and after the test and compared these amounts with each other. In another words, a slice of the liver was picked up soon after installation of anesthesia and its amount of glycogen was measured. 120 minutes later, the same procedure was done and the amount of liver glycogen was measured. In the control experiments of normal dogs, the amount of hepatic glycogen decreased in all cases after the test. Contrary to these experiments, in the totally pancreatectomized dogs, an increase in liver glycogen content was recognized in four cases out of seven, as shown in Table 3 and Fig. 6 and the other 3 cases showed a decrease of less degree than control cases.

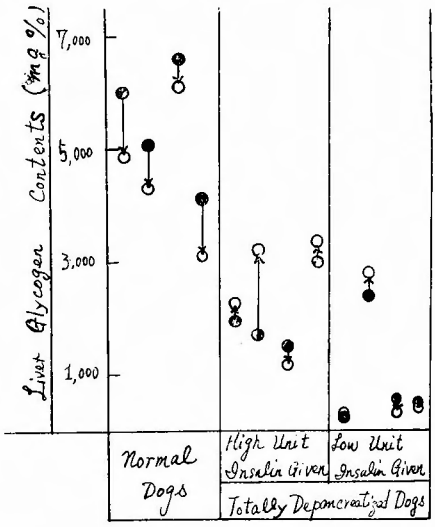


Fig. 6 Decrease or Increase in Liver Glycogen Contents by Insulin Injection in Normal Dogs and Totally Depancreatized Dogs
●: Liver Glycogen Contents Before Insulin Injection
○: Liver Glycogen Contents At 120 minutes After Insulin Injection

v) Insulin Test after The 4th Postoperative Week

After more than four weeks had elapsed since total pancreatectomy, I examined

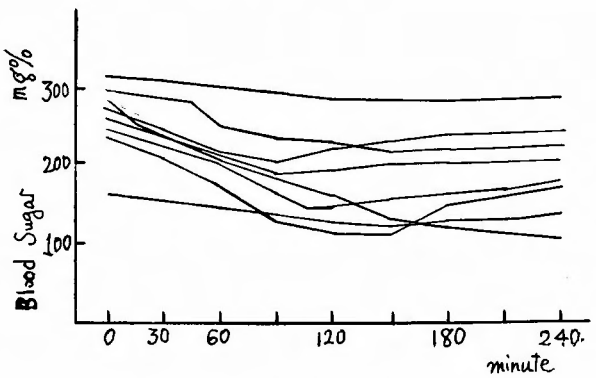


Fig. 7 Blood Sugar Curves After Insulin Injection in Totally Depancreatized Dogs After 4th Postoperative Week
(Dose of Insulin: 0.1~0.3 u/kg Intravenously injected)

insulin test and determined liver glycogen contents. In this period, totally depancreatized dogs were apt to develop hypoglycemic signs. Liver glycogen contents were measured in twelve cases including two which were alive for more than two months. At the same time, if possible, insulin test was performed and assimilation index was calculated. The hypoglycemic signs appeared in six cases out of 12 a few days before or after the insulin test. The curve of blood sugar by insulin test in those days was shown in Fig. 7 and it was almost similar to that in the 3rd week. In the cases in which the hypoglycemic signs were shown, their assimilation indices were found to be 0.14-0.43. On the other hand, in the other cases in which the hypoglycemic signs were not recognized, their assimilation indices were 0.07-0.32. Therefore, as far as assimilation index was concerned, there was no difference in particular between these two groups as shown in Table 4. Moreover, as shown in Table 5, the insulin test was performed two times, viz. before and after the 3rd postoperative week, on one and the same case with the results that every depancreatized dogs had its own stabilized assimilation index not influenced by either the elapse of time after the operation or occurrence of hypoglycemic signs.

vi) Liver Glycogen after The 4th Postoperative Week

Liver glycogen contents were 250mg%-3,300mg% after the 4th postoperative week as shown in Table 6 and Fig. 9 and two-thirds out of 12 cases showed more than 1,000 mg %. These values were within quite the same range as that which was shown at the 3rd postoperative week in those cases given a large amount of insulin. If treated adequately with insulin, long-lived dogs could keep the normal values of the liver glycogen showing 2,000 mg% -3,000mg% throughout their postoperative course, even if hypoglycemic signs

Table 4 Assimilation Indices in Totally Depancreatized Dogs after the 4th Postoperative Week

Assimilation Index	
Cases with Hypoglycemic Sign	Cases without Hypoglycemic Sign
0.427	0.320
0.256	0.209
0.241	0.195
0.136	0.106
	0.068

Table 5 Assimilation Indices Obtained by Insulin Tests which Performed Two Times on One and the Same Dog

Dog No. \ Week	I	II	III	IV	V	VI
18		0.50		0.37		
77			0.16		0.40	
82		0.28				0.21
M1		0.50			0.45	
M3		0.45				0.35
M4		0.10		0.11		
M7		0.31			0.42	

Table 6 Liver Glycogen Content in Totally Depancreatized Dogs after the 4th Postoperative Week

Liver Glycogen Content	
Cases with Hypoglycemic Sign	Cases without Hypoglycemic Sign
3,315mg%	2,018mg%
2,290	1,556
2,070	1,271
1,620	1,120
1,380	981
533	233

sometimes occurred. Therefore, against invasive procedures such as surgical operations, the depancreatized dogs had the qualification to be responsive nearly the same as the normal dogs. In these times, assimilation indices by insulin test were 0.07-0.43 as I stated before showing almost the same values as at the 3rd week. Moreover, if those dogs were divided into two groups, the one which showed hypoglycemic signs and the other which did not show, as shown in Table 6, the liver glycogen contents were found to be 3,300 mg%-500mg% in the former, and 1,600 mg%-200mg% in the latter.

From the results of the above tests, relations between liver glycogen contents and assimilation indices were given as shown in Fig. 8, 9, & 10.

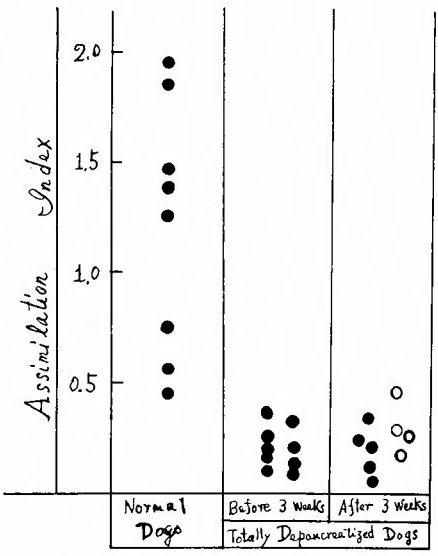


Fig. 8 Assimilation Indices Obtained from Normal Dogs and Totally Depancreatized Ones.
○ : Showing Dogs in which Hypoglycemic Sign Occurred

As the time was passing by after total pancreatectomy, even if hypoglycemic signs were easy to develop in later periods, any changes hardly could be seen in assimilation index (Fig. 8), and liver glycogen contents did not always decrease extremely (Fig. 9). Furthermore, it was hard to find out any interrelations between the assimilation indices and the amounts of liver glycogen, the former having shown their own values in individual cases (Fig. 10).

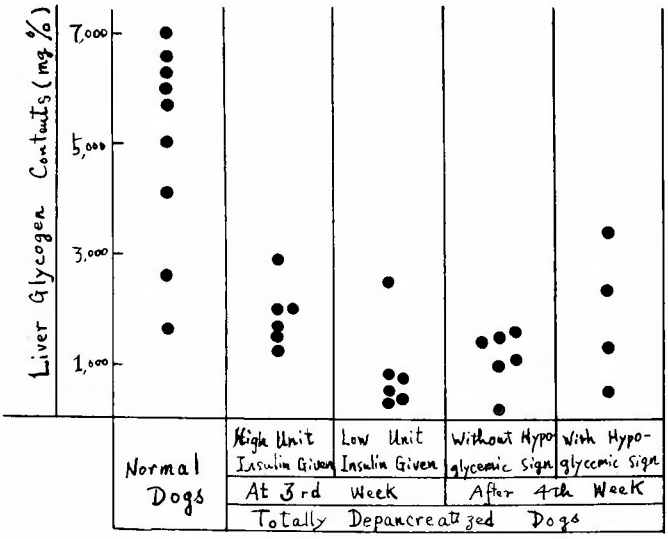


Fig. 9 Liver Glycogen Content in Normal and in Totally Depancreatized Dogs

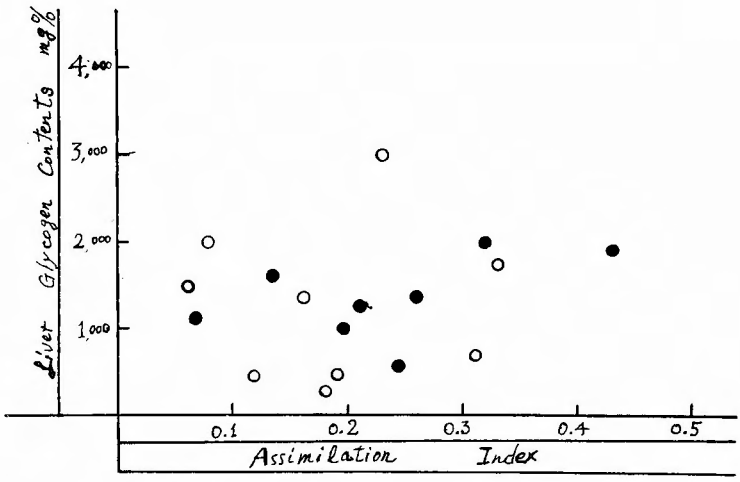


Fig. 10 Relations between Assimilation Indices and Liver Glycogen Contents in Totally Depancreatized Dogs

○ Showing Dogs at 3rd Postoperative Week

● Showing Dogs After 4th Postoperative Week

IV. DISCUSSION

It is generally assumed that an increase of insulin sensitivity is shown after total pancreatectomy. Contrary to this assumption, the insulin sensitivity was found to be lowered according to the calculation on assimilation index in our clinic. While the hypoglycemic signs were seen by the administration of 2.0 units of insulin per kg in body weight after the 4th postoperative week, the assimilation index was found to be lowered, thus indicating the decreased sensitivity. How to understand these contradictory phenomena?

Insulin test is performed with the purpose to evaluate the activity of injected insulin which accelerates the utilization of dextrose in tissues. NORGAARD-THAYSEN divided the blood sugar curve obtained by insulin injection into two parts, calling the downward part "Assimilation Line" and the upward part "Restoration Line." This restoration line is based upon the action to restore the state of hypoglycemia in the anti-insulin system. Hypoglycemic symptoms seemed to be provided not only by the blood sugar lowering action of insulin but rather by the hypoglycemia-restoring activity.

Although it is very natural to call it insulin-sensitive if remarkable hypoglycemic symptoms occur under the administration of a small amount of insulin, it must be admitted that the assimilation index is not always increased under these circumstances. The words "Insulin Sensitivity" would rather mean the descending velocity of the blood sugar level after the injection of insulin. In totally depancreatized ones in which hypoglycemic symptoms are recognized after the injection of a small amount of insulin, it could not be said that they are sensitive to insulin, but be said that they have not an ability to restore the hypoglycemia. In otherwords, they are in the state of hypoglycemia unresponsiveness as termed by FRASER, ALBRIGHT and

SMITH, and according to my study, their sensitivity to insulin was found to be lowered. Formerly HASEGAWA in our clinic examined the anterior pituitary of depancreatized dogs histologically demonstrating the hypofunction of this organ, and AOKI in the same clinic found the hypofunction of the adrenal cortex in these dogs. These data supports the conception of hypoglycemia unresponsiveness stated above.

It is usually believed that the blood sugar level was mostly regulated by the liver. In 1938 SOSKIN and others made an experiment and stated that when the level of blood sugar rose the liver took up the blood sugar making its level low; and when the blood sugar level dropped, the liver discharged its sugar to the blood stream making the blood sugar level high, and thus keeping the blood sugar at a certain level. Afterwards, the results of the above experiment was assured by the method of liver cathetelisation and application of bromsulphalein.

In diabetes mellitus, it could be well imagined that the liver glycogen (sugar storaged in the liver) is extinguished, because the blood sugar level is kept high and much sugar is excreted in the urine. In the case of total pancreatectomy, it was acknowledged by HINSELMANN, FISHER, LACKEY, MACLEOD, MITSUNAGA and others that liver glycogen could hardly be found 48-72 hours after the operation.

On the other hand, it was reported that the amount of liver glycogen was restored to normal state by the insulin therapy. In my experiment also, it was demonstrated that the totally pancreatectomized dogs could keep the amount of liver glycogen in normal state if they were treated with an adequate amount of insulin having a good appetite, throughout and even after the 4th postoperative week. But from the results of my experiment, it seemed that the ability to possess the glycogen in the liver was somewhat restricted in the totally depancreatized dogs, and was not quite the same as in normal dogs.

As to the fatty liver, MACLEOD and others pointed out that its later type which was developed several weeks after total pancreatectomy did not fade away any longer even though the insulin therapy was continued, and accordingly suggested the decrease of liver glycogen in these cases. To the contrary, I could not admit such a finding as already stated above.

Then I examined the relationships between liver glycogen contents and insulin sensitivity. In diabetes mellitus, FORSGREN stated that insulin sensitivity was decreased when liver glycogen was abundant and when liver glycogen was scanty, insulin sensitivity was increased. Also FALTA and ÜBERRAK examined the transition of the level of blood sugar and the amount of sugar excreted in the urine related to the time. They discussed sensitivity based on hypoglycemic sign and stated that the insulin sensitivity was demonstrated in its maximum when the amount of glycogen in the liver was in minimum, in the so-called "skretorisch" (dissimilatorisch) stadium. Also SOSKIN and LEVINE declared, in their writings "Carbohydrate Metabolism," that if the liver glycogen was less than usual the hypoglycemic signs were apt to be developed. Despite these opinions, I could not find out any relationships between liver glycogen and the development of hypoglycemic sign. Moreover, adding to my finding, KITANI reported that a considerable amount of glycogen was kept

even in the cases of hyperinsulinism.

It was already demonstrated by HASEGAWA that the endocrine activity of the pituitary gland in dogs was lowered after total pancreatectomy and that these dogs operated on were coming near to HOUSSAY's dogs whose depancreatogenic diabetes mellitus was decreased in its severity by subsequent resection of the pituitary gland. This assumption was endorsed by the fact that the blood sugar curves of the depancreatized dogs obtained by the injection of insulin after the 4th postoperative week showed almost the same type as that of HOUSSAY's dogs. In HOUSSAY's dogs, moreover, hypoglycemic signs are apt to be developed. According to the experiments of CHAIKOFF, GIBBS, HALTON and REICHERT, in the hypophysectomized and totally pancreatectomized dogs, it was demonstrated that a considerable amount of glycogen was kept in the liver even though the amount of fat in the liver was increased. The same results were also obtained in my study.

When the totally depancreatized dogs are treated adequately with the administration of insulin, these dogs are found to be coming near spontaneously to HOUSSAY's dogs can be alive further keeping the amount of liver glycogen in almost the normal level and showing the individually definite sensitivity to insulin, even if there is a possibility of developing hypoglycemic shock.

V. CONCLUSIONS

I performed total pancreatectomy on the adult dogs, and investigated the relationships between insulin sensitivity and liver glycogen contents following the postoperative course. The results are as follows;

1) Assimilation indices of totally depancreatized dogs were calculated throughout the postoperative course these indices were found to be lower than those of normal dogs showing the dropping of sensitivity to insulin.

2) The terms "Insulin sensitivity" must be limited in its usage, only to mean the insulin action to lower the level of the blood sugar. As to the assimilation index obtained by insulin test, the same consideration must be taken. Therefore, in most of the totally depancreatized dogs, they are not sensitive to insulin, but in the state of hypoglycemia unresponsiveness.

3) Hypoglycemic symptoms in the totally depancreatized dogs have no close relationships with insulin sensitivity which is shown by assimilation index, but they must be discussed under the hypoglycemia unresponsiveness and re-adjustment of the endocrine system.

4) The totally depancreatized dogs, in the 3rd postoperative week, keep the amount of liver glycogen at almost the normal level under the administration of 20 units or more of insulin per kg in body weight, and they have a considerable degree of resistance against the exogenic stresses, such as surgical opration or general anesthesia.

5) If treated with insulin adequately, even after the 4th postoperative week, the blood sugar level in totally depancreatized dogs is controlled fairly well and their liver glycogen content is kept at almost the normal level.

6) No relationships between assimilation index and liver glycogen content can be seen. It is suggested that the results of insulin test in totally depancreatized dogs is not simply influenced by the liver, but mostly by the postoperative internal environment presented by all of the endocrine organs related to sugar metabolism.

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和 文 抄 録

膵全剔犬に於けるインシュリン感性と肝糖原量との関係について

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膵全剔犬及び人体例は，インシュリンに対し感受性が増強しており，屢々低血糖症状を呈すると云うのが一般の通説であつた．これ対し，当教室の河村は，インシュリン・テストを行ない，同化率を計算し，膵全剔犬及膵全剔人体例は，インシュリンに対し，むしろ鈍感になつている事を報告した．

著者は，膵全剔犬に対し，各種インシュリン・テストを行ない，インシュリン感性と，低血糖症状発現の関係を追求した．これと同時に，血糖供給の主役を演ずる肝糖原の変動を測定し，インシュリン感性度との間に如何なる関係があるか検索した．

そして次の如き結果を得た．

膵全剔術後，全経過に於いて，同化率は明らかにインシュリン鈍化と解すべき結果を得た．低血糖症状は術後第4週目以後に於いて発来するのを認めた．この低血糖症状の発来の有無にかゝわらず，術後経過に従つて検索しても，インシュリン・テストによる同化率には変化を来たす様な事はなく，被検犬は，夫々固有の値を有している．そして，その値と低血糖発来との間には，何等の関係も認める事は出来なかつた．膵全剔犬は iusulin sensitive と云うより，hypoglycemia unresponsiveness 即ち低血糖恢復力の減弱を認めるのである．又このために低血糖症状を来たすのである．

又，膵全剔犬は，術後第3週目の経験に於いて，高単位インシュリン治療群（3.0～5.0単位/kg投与群）と低単位インシュリン治療群(1.0単位/kg投与群）とを比較すると，前者は一般に肝糖原量が多く，正常値に保持されている．これに対し，低単位投与群は，可成り低値を示す．更に，術後第4週目に至るも，適度のインシュリン療法（2.0単位/kg投与）と，食思が充分に保たれるならば，たとえ低血糖症状を発来するにしても，正常値近くに肝糖原は保持されている．これも麻酔・開腹等の外来性の侵襲に対し，正常犬とほゞ等しい抵抗を示す．

最後に，肝糖原量と同化率との関係をみると，この両者間には一定の関係を見出す事は困難である．即ち膵全剔犬のインシュリン・テストの成績は，単に肝の影響を受ける以上に，膵全剔の各内分泌系の作用に支配される事がうかがわれる．